

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/70924

<p><b>A. CLASSIFICATION OF SUBJECT MATTER</b></p> <p>IPC(8) - A61K 31/498; A61K 31/4406 (2008.04)</p> <p>USPC - 514/266.24; 514/357</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>																						
<p><b>B. FIELDS SEARCHED</b></p> <p>Minimum documentation searched (classification system followed by classification symbols)</p> <p>USPC: 514/266.24; 514/357</p>																						
<p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>USPC: 514/266.24; 514/357 (text search)</p>																						
<p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)</p> <p>Electronic Databases: (USPT, JPA, EPAB, PGPB); Google Scholar</p> <p>Search Terms: HDAC Inhibitor, MS-275, CI-994, anti-EGFR, Gefitinib, imatinib, Gleevec, epithelial origin, breast, colon, head and neck, pancreas, E-cadherin</p>																						
<p><b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b></p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td>WITTA et al. Restoring E-Cadherin Expression Increases Sensitivity to Epidermal Growth Factor Receptor Inhibitors in Lung Cancer Cell Lines, <i>Cancer Research</i>, 15 Jan 2006, Vol 66, No 2, pp 944-950 (p 944, abstract; pg 948 Fig 5).</td> <td>1-7</td> </tr> <tr> <td>Y</td> <td>KRAKER et al. Modulation of histone acetylation by [4-(acetylamo)-N-(2-amino-phenyl)benzamide] in HCT-8 colon carcinoma, <i>Mol. Cancer Ther.</i>, April 2003, Vol 2, No 4, pp 401-8. (p 401, abstract).</td> <td>5-7</td> </tr> <tr> <td>Y</td> <td>NIMANNAPALLI et al. Histone Deacetylase Inhibitor LAQ824 Both Lowers Expression and Promotes Proteasomal Degradation of Bcr-Abl and Induces Apoptosis of Imatinib Mesylate-sensitive or -refractory Chronic Myelogenous Leukemia-Blast Crisis Cells, <i>Cancer Research</i>, 15 Aug 2003, Vol 63, No 16, pp 5126-35. (p 5126, abstract; pg 5132, Fig 5A).</td> <td>8-10</td> </tr> <tr> <td>Y</td> <td>MATEI et al., Imatinib mesylate (Gleevec) inhibits ovarian cancer cell growth through a mechanism dependent on platelet-derived growth factor receptor alpha and Akt inactivation, <i>Clinical Cancer Research</i>, 15 January 2004, Vol 10, No 2, pp 681-690 (p 681, abstract; p 681, para 1).</td> <td>8-10</td> </tr> <tr> <td>Y</td> <td>MENDELSOHN et al. Status of Epidermal Growth Factor Receptor Antagonists in the Biology and Treatment of Cancer, <i>Journal of Clinical Oncology</i>, 15 July 2003, Vol 21, No 14, pp 2787-2799. (p 2787, abstract; pg 2791, col 2, para 1-2; pg 2792, col 1, para 3).</td> <td>1-4</td> </tr> <tr> <td>Y</td> <td>EGER et al. DeltaEF1 is a transcriptional repressor of E-cadherin and regulates epithelial plasticity in breast cancer cells, <i>Oncogene</i>, 31 March 2005, Vol 24, No 14, pp 2375-85. (p 2375, abstract).</td> <td>1-4</td> </tr> </tbody> </table>		Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	WITTA et al. Restoring E-Cadherin Expression Increases Sensitivity to Epidermal Growth Factor Receptor Inhibitors in Lung Cancer Cell Lines, <i>Cancer Research</i> , 15 Jan 2006, Vol 66, No 2, pp 944-950 (p 944, abstract; pg 948 Fig 5).	1-7	Y	KRAKER et al. Modulation of histone acetylation by [4-(acetylamo)-N-(2-amino-phenyl)benzamide] in HCT-8 colon carcinoma, <i>Mol. Cancer Ther.</i> , April 2003, Vol 2, No 4, pp 401-8. (p 401, abstract).	5-7	Y	NIMANNAPALLI et al. Histone Deacetylase Inhibitor LAQ824 Both Lowers Expression and Promotes Proteasomal Degradation of Bcr-Abl and Induces Apoptosis of Imatinib Mesylate-sensitive or -refractory Chronic Myelogenous Leukemia-Blast Crisis Cells, <i>Cancer Research</i> , 15 Aug 2003, Vol 63, No 16, pp 5126-35. (p 5126, abstract; pg 5132, Fig 5A).	8-10	Y	MATEI et al., Imatinib mesylate (Gleevec) inhibits ovarian cancer cell growth through a mechanism dependent on platelet-derived growth factor receptor alpha and Akt inactivation, <i>Clinical Cancer Research</i> , 15 January 2004, Vol 10, No 2, pp 681-690 (p 681, abstract; p 681, para 1).	8-10	Y	MENDELSOHN et al. Status of Epidermal Growth Factor Receptor Antagonists in the Biology and Treatment of Cancer, <i>Journal of Clinical Oncology</i> , 15 July 2003, Vol 21, No 14, pp 2787-2799. (p 2787, abstract; pg 2791, col 2, para 1-2; pg 2792, col 1, para 3).	1-4	Y	EGER et al. DeltaEF1 is a transcriptional repressor of E-cadherin and regulates epithelial plasticity in breast cancer cells, <i>Oncogene</i> , 31 March 2005, Vol 24, No 14, pp 2375-85. (p 2375, abstract).	1-4
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>																						
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>																						
Date of the actual completion of the international search	Date of mailing of the international search report																					
25 September 2008 (25.09.2008)	07 OCT 2008																					
Name and mailing address of the ISA/US	Authorized officer:																					
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774																					

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**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: 11-61  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.